REMARKS

This is responsive to the Office Action mailed December 2, 2004. Claims 1-10 and 39 have been canceled and replaced therewith new Claims 40-46. Claims 27-38 have been canceled as they are non-elected claims. Claim 11 has been amended to make the process claim depend from the protein complex claim 40. Thus, Claims 11-26, and 40-46 are currently pending in the application.

The amendments and new claims are fully supported in the specification and no new matter has been added. Entry of the amendment in Claim 11 and the new claims 40-46 and reconsideration of the rejections in view of the new claims are respectfully requested.

In addition, Table 1 of the specification has been amended as shown in page 3 of this Amendment. Specifically, wherever relevant in the table, the stop amino acid number in the Amino Acid Coordinates of survivin has been changed from "143" to "142". This is to amend an obvious error – The protein Survivin only has a total of 142 amino acids. This amendment does not add new matter because "143" is an obvious error in view of the other parts of the Specification which clearly provide the correct amino acid coordinates ending with "142". *See* Specification, page 23 at line 7 (providing amino acid coordinate 89-142), line 10 (aa 99-142), line 25 (aa 3-99 and 47-142), line 29 (aa 3-99 and aa 89-142), and line 27 (stating that "survivin is 142 amino acids long"). Entry of this amendment is respectfully requested.

I. Claim Objections

Claims 1, 2, 4, 5 and 7 are objected to for informalities within the claim language with regard to non-elected subject matter. The claims have been canceled, and replaced by new Claims 40-46. The new claims do not contain the non-elected subject matter objected to. Thus, the objection has been obviated.

II. Specification Objections

The specification is objected to for not including the U.S. Provisional Application number for the said application filed on October 25, 2001. Applicants have amended the

specification to include the proper information. Applicants have also attached a new Declaration which includes the proper priority information.

The specification is also objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants have reviewed the entire specification and have deleted the hyperlinks contained therein and replaced therewith relevant information. No new matter has been added.

III. The New Claims Are Clear and Definite.

The now canceled claims 1-5, 7 and 39 stand rejected under 35 USC § 112, ¶2 as being indefinite. Specifically, the Office Action asserted that the terms "homologue" and "derivative" were vague. Applicants respectfully traverse. Specifically, the terms are clearly defined in the Specification, e.g., at page 17, second paragraph and page 18, second paragraph. Regardless, while the subject matter covered by the terms may still remain, the new Claims 40-46 do not contain the terms "derivative" and "homologue." Thus, this rejection has been obviated.

IV. The New Claims Satisfy the Written Description Requirement.

Claims 1 through 5, 7 and 39 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 1-5, 7 and 39 have been canceled and replaced therewith Claims 40-46. To the extent that the same rejection would be applied to Claims 40-46, Applicants respectfully traverse.

The new claims now recite a polypeptide having an amino acid sequence at least 90% identical to that of the native sequence (e.g., survivin), and that interacts with the native interactor (e.g., HDLC1) of the native sequence. Applicants note that this is analogous to the "product by function" claim in Example 14 of the Revised Interim Written Description Guidelines Training Materials (hereinafter "Training Materials"). *See* page 53 of the Training Materials.

Specifically, the claim in Example 14 of the Training Materials defines a protein variant by (1) sequence identity and (2) its activity (catalytic activity). Likewise, for

example, in Applicants' new Claims 40-46, each of the first protein and second protein is defined by (1) sequence identity and (2) its activity (i.e. binding/interaction).

In Example 14 of the Training Materials, the specification discloses a single species of the claimed protein genus. "The specification also **contemplates but does not exemplify variants of the protein** wherein **the variant can have any or all of the following: substitutions, deletions, insertions and additions.** The specification indicates that **procedures for making proteins with substitutions, deletions, insertions and additions is routine in the art** and **provides an assay for detecting the** catalytic **activity of the protein.**" (*USPTO Revised Interim Written Description Guidelines Training Materials*, page 53, emphasis added.)

In the instant case, the Applicants have discovered that two proteins – survivin and HDLC1 – specifically interact with each other. *See* Specification, pages 21-25. Specific exemplary fragments of the interacting proteins capable of interaction with the native interacting partner are also disclosed. *See* Specification, pages 21-25, particularly Table 1 at page 21 and page 23 at lines 7, 12 and 25.

The specification also teaches in details methods of providing homologues and fragments of such interacting species by (1) sequence alignment and analysis of ortholog sequences (*see* Specification at page 17, lines 11-16, and lines 22-30, and page 18, lines 1-12), and (2) mutagenesis (i.e. substitutions, deletions, insertions and additions) (*see* Specification, page 17 at lines 16-21, page 27 at lines 16-29, page 28 at line 13-21, page 29 at lines 6-14, and page 34 at lines 5-14). These methods for generating variants are routine in the art. As generally known to a skilled artisan, substitutions lead to homologues, deletions lead to fragments, while additions result in fusion proteins.

In addition, the Specification also provides assays for determining the activity of such variants (i.e. the binding affinity to the interacting partner). *See* Specification, page 17 at lines 18-21, page 20 at lines 1-9, page 27 at lines 20-29, page 28 at lines18-21, page 29 at lines 11-14, particularly the binding assays in pages 54-57, and two-hybrid assays in pages 57-72 and Example 1 at pages 118-119 and Example 3 at pages 120-121. Indeed, such and other assays for protein-protein interactions are routine and well-known in the

art. These assays are much more routine and predictable than the enzymatic assays in Example 14 of the Training Materials, if comparable at all.

Thus, each and every elements of the claimed protein complex is described as adequately as the claim elements in Example 14 of the Training Materials are. The Training Materials, having been recognized by the Federal Circuit, provides clear guidance in the particular situation in the instant case. The Example 14 in the Training Materials makes it amply clear that Applicants' new Claims 40-46 sufficiently meet the written description requirement. Accordingly, the rejection in this respect should be withdrawn.

V. The New Claims Meet the Enablement Requirement

Claims 1 through 5, 7 and 39 are rejected under 35 U.S.C. § 112, ¶ 1, as allegedly being not enabled. To the extent that the same rejection would be applied to the new Claims 40-46, Applicants respectfully traverse.

What is required under the enablement requirement is that an ordinarily skilled person in the art, reading the specification and in view of prior art knowledge, would be able to reduce the claimed invention to practice without undue experimentation. Note that certain degree of experimentation is always allowed – otherwise, patents would issue only with claims direct to "literally disclosed" species in the specification. If this were the case, few would be willing to file for patent protection.

In the instant case, a reasonable molecular biologist would readily recognize that if Applicants were given only claims directed to a protein complex formed by the native full-length proteins, any molecular biologists would be able to easily design around the patent by making substitutions, insertions or deletions in the native proteins. Applicants would be better off by not filing the patent application but keeping the knowledge of protein-protein interaction as trade secret.

Indeed, the mere knowledge that the two native proteins interact would enable an ordinarily skilled person to make the variants of the native proteins as defined by the new claims, even without reading Applicants' specification. Making substitutions, insertions or deletions in the native proteins does not require undue experimentation, and testing the

resulting variants for their binding affinities using any protein-protein interaction assay is even more routine.

What does this mean? It is simple – the protein complexes formed by the variants generated by substitutions, insertions and deletions in the native proteins are inherently enabled to an ordinarily skilled artisan.

The Office Action asserted that there is high unpredictability in changes to a protein sequence. This is true with respect to individual amino acid residues within a protein sequence. As a matter of fact, as shown in the attached article (Yang *et al.*, *Biochemistry*, 40:3943-3950 (2001), Exhibit A), the correlation between amino acid sequence and enzymatic activity can be extremely unpredictable. For example, in the eNTPDase-3 taught in Exhibit A, mutations such N191A, Q226A, and R67G resulted in an increase in the enzymatic activity. The R146P mutation essentially converted the eNTPDase-3 ecto-apyrase to an ecto-ATPase (eNTPDase-2). The Q226A mutant exhibited a change in the divalent cation requirement for nucleotidase activity relative to the wild-type and the other mutants. The E182D mutation, albeit conservative, completely abolished enzymatic activity.

Even with such unpredictability, the Training Materials implicitly indicates that the claim in Example 14 of the Training Materials is allowable – which is indeed the PTO's routine practice. Certainly, finding variants retaining the native binding activity is no more unpredictable than generating variants retaining the native enzymatic activity.

Regardless, Applicants note that the Office Action's focus on predictability at the individual amino acid residue level is misplaced. As shown in the above discussed Exhibit A, it is true that changes to particular individual amino acid residues are unpredictable in terms of the resulting protein activity – only when each and every single amino acid residue is investigated the correlation between the residues and the protein activity is deciphered. However, what is highly **predictable** is that one can, with great certainty, generate protein variants/fragments that still retain the activities of the native protein, e.g., binding activity or catalytic activity.

Particularly, one of ordinary skill apprised of Applicants' disclosure will predictably be able, by routine deletions, insertions and/or substitutions techniques, to

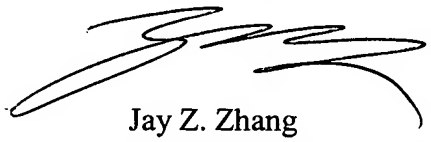
make the variants called for in the new Claims 40-46 that can form the claimed protein complex. Accordingly, Applicants respectfully submit that the new Claims 40-46 are adequately enabled. The rejection in this respect should be withdrawn.

CONCLUSION

New Claims 40-46 are in condition for allowance, and an early notice thereof is respectfully solicited. Should the Examiner determine that additional issues remain which might be resolved by a telephone conference, he is respectfully invited to contact Applicants' undersigned attorney.

It is not believed that any time extension or fees are required with this response. If this is incorrect, an extension of time as deemed necessary is hereby requested, and the Commissioner is hereby authorized to charge any appropriate fees or deficiency or credit any over payment to Deposit Account no. **50-1627**.

Respectfully submitted,



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